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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,009	SHARIFI ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *October 27, 2006, November 15, 2006 and December 21, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on April 23, 2009, is acknowledged.

Applicant has elected the invention of Group II, claim(s) 2-4 and 6-8, drawn to a method of transdifferentiating a monocytic cell into an endothelial cell, comprising: providing a monocytic cell transduced with a retrovirus expressing PTN, thereby artificially increasing the expression of PTN in the monocytic cell such that the transgenic monocytic cell transdifferentiates into an transgenic endothelial cell.

Within Group II, Applicant has elected the compound species that either increases or decreases endogenous PTN activity to be a small molecule.

Because Applicant did not distinctly and specifically point out the supposed errors in the Group restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP §818).

Election of Applicant's species was made with traverse.

Applicant argues that Applicant's do not believe that an election of species is applicable to Claims 1-8, particularly in light of Applicant's election of Group II, drawn to a method of transdifferentiating a monocytic cell into an endothelial cell, comprising: providing a monocytic cell transduced with a retrovirus expressing PTN, thereby artificially increasing the expression of PTN in the monocytic cell such that the transgenic monocytic cell transdifferentiates into an transgenic endothelial cell.. The Examiner finds this argument persuasive and withdraws the species election with the understanding that the retrovirus expressing PTN, thereby artificially increasing the expression of PTN in the host cell, is the "compound" that increases PTN activity.

Claims 9-10 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-8 are under consideration.

Priority

This application is a 371 of PCT/US04/22827 filed July 15, 2004. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/487,409, filed on July 15, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on October 27, 2006, November 15, 2006 and December 21, 2006 that have been considered.

The references cited in the IDS filed December 21, 2006 are lined through because they are duplicates of the references cited in the IDS filed October 27, 2006.

The Souttou reference (IDS filed December 21, 2006) is also lined through because it does not comply with 37 CFR 1.98(b) requiring that each item of information in an IDS be identified properly. However, the Examiner notes that the Souttou reference is properly cited in the IDS filed October 27, 2006.

The signed and initialed PTO Forms 1449 are mailed with this action.

Drawings

1. **New corrected drawings in compliance with 37 CFR 1.121(d) are required** in this application because Figures 3B, 5C, 5D, 5E and 5F do not photocopy well, yielding essentially opaque panels, and thus precluding the artisan and the Examiner from evaluating the data on its merit. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

2. **Claims 1 and 5 are objected to because of the following informalities**:

These claims each identify "PTN" as a polypeptide to be used in the claimed invention. However, the claims do not first identify the polypeptide by its complete name prior to using its acronym. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses, e.g. Epidermal Growth Factor (EGF).

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. **Claims 5-8 are rejected under 35 U.S.C. 101** because the claimed invention is directed to non-statutory subject matter. The claims are directed to "endothelial cells" transduced with the claimed viral vector, without restriction as to where the cell is located. The scope of invention as claimed embraces a genetically modified human carrying in its genome or at least some of their cells a recombinant genetic material. Applicant's intended use of the monocytes transfected with a nucleic acid encoding PTN, thereby inducing differentiation into endothelial cells comprises promoting neovascularization to treat diseases such as ischemia by enhancing or promoting the activity of PTN (pg 8, ¶3). It is implicit that such patients are mainly human. Consequently, when read in light of the specification the claimed host cells would include host cells in human patients that would be an integral and inseparable part of the human. Such cells that are part of a human are non-statutory subject matter since they embrace the human that carries them. It is USPTO policy not to allow claims to humans (1077 O.G. 24 April 1987). See MPEP §2105.

The claims should be amended by insertion of "isolated" before "endothelial cells".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

4. **Claims 1 and 5 are rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the means by which the expression of PTN is artificially increased in the monocytic cell such that the monocytic cell transdifferentiates into an endothelial cell.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. **Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method of transdifferentiating a monocytic cell into an endothelial cell, the method comprising transducing the monocytic cell *in vitro* with a retrovirus expressing PTN such that the monocytic cell transdifferentiates into an endothelial cell, and an endothelial cell produced by said method, does not reasonably provide enablement for an enormous genus of artificial means of increasing the expression of PTN in the monocytic cell, nor transducing the monocytic cell *in vivo* with a retrovirus expressing PTN. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claims reasonably embrace *in vivo* gene therapy, which involves one of the most complex and unpredictable areas of medicine molecular biology. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims also reasonably embrace a multitude of structurally distinct agents, i.e. small molecules, peptides or drugs (pg 8, ¶4), intended to increase the expression of PTN in the monocytes to cause transdifferentiation into endothelial cells.

The inventive concept of the instant application is that in the presence of PTN, monocytic cells transdifferentiate into endothelial-like cells (pg 9, ¶2).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification discloses the *in vitro* transduction of RAW and THP-1 cell lines with a retroviral vector encoding PTN. The level of αvβ3 integrin in the PTN-expressing THP-1 cells is similar to those of human coronary artery endothelial cells, as determined by FACS analysis (pg 11, ¶2). PTN expression led to up-regulation of both GATA-2 and GATA-3 transcription factors (endothelial cell markers) in THP-1 cells at the levels comparable to those of control human endothelial cells (pgs 11-12, joining ¶).

However, the claims are not enabling for methods of transducing monocytic cells *in vivo* with a retrovirus encoding PTN because the specification fails to disclose how the artisan is to administer and specifically target the monocytic cells with said retrovirus. Instead, the *in vitro* transfected RAW or THP-1 cells expressing PTN (Figure 5E; Figure 6; Figure 7) are injected into animal models.

The claims are also not enabled for the multitude of structurally distinct agents, i.e. small molecules, peptides or drugs (pg 8, ¶4), intended to increase the expression of PTN in the monocytes to cause transdifferentiation into endothelial cells because the specification fails to disclose the structural identity of such agents, *in vitro* working examples demonstrating that such an agent predictably induces the expression of PTN in a monocyte to induce transdifferentiation, how to administer the proper dose of said agent *in vivo*, nor how to specifically target monocytes *in vivo* with a delivery vehicle comprising said agent.

The State of the Prior Art

Applicant contemplates that the recombinant nucleic acid composition may be introduced *in vivo*, and thus Applicant's invention falls within the realm of gene therapy, which is in the nature of transforming cells with nucleic acids encoding therapeutic molecules to produce a therapeutic effect. Applicant further claims that the nucleic acid vector may be a virus. In view of the state of the art and the level of the skilled in gene therapy art, it is still under development and highly unpredictable. Orkin et al (National Institutes of Health Report, December 7, 1995) reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were:

1) gene therapy for each disease would present its own scientific and clinical challenges;

2) no successful gene therapy protocol was known;

3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors;

4) basic studies of disease pathology, which are likely to be critical to the eventual success of gene therapy, have not been given adequate attention, so as to better define the important target cell(s) and to more effectively design the therapeutic approach;

5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; and

6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints (pages 1-2).

Although the reference is ages old, the general status of gene therapy art has not significantly changed. Patterson (STATEMENT OF AMY PATTERSON M.D., February 2000) reviews "The success of this technology [gene therapy] is dependent upon not only the delivery of genetic material into the target cells, but also the expression of the gene once it reaches its target site. Both of these requirements pose considerable technical challenges". Patterson further teaches that out of 372 clinical trials registered with the NIH, only one percent of the trials (3) have progressed to Phase III efficacy studies. "For this reason, it is perhaps more accurate to refer to this technology as 'gene transfer', rather than 'gene therapy', until there is more evidence for the therapeutic benefit of this technology".

Applicant only discloses working examples of the invention using *in vitro* cell culture conditions. However, one of ordinary skill in the art recognizes that *in vitro* conditions do not reasonably extrapolate to *in vivo* conditions because for *in vitro* methods, an artisan has significantly greater control over access to a chosen cell type and the ability to optimize the amount of, and the means by which, the recombinant nucleic acid is delivered to the chosen cell population, which are not identically transferable to *in vivo* conditions. Rather, for *in vivo* methods, an artisan must consider method steps to optimally deliver a therapeutically effective amount of the recombinant nucleic acid to the chosen cell, organ or tissue type, e.g. nerve cells, endothelial cells, hematopoietic cells, muscle, brain, liver, heart, colon, pancreas, kidney, etc, wherein each chosen cell, organ or tissue type demands distinctly different, non-identical cell biological and physiological considerations, e.g. route of administration, to achieve the necessary incorporation of the recombinant nucleic acid and effect the desired therapeutic result.

With regard to gene therapy, at the effective filing date of the present application, the attainment of any therapeutic effect via gene therapy was, and remains, highly unpredictable, let alone for the attainment of prophylactic effects via gene therapy mechanisms as contemplated by Applicants. While progress has been made in recent years for gene transfer *in vivo*, vector

targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. There are several known factors that limit an effective human gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells. For example, Deonarain (Expert Opin. Ther. Pat. 8: 53-69, 1998) indicates that:

> "[O]ne of the biggest problems hampering successful gene therapy is the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (page 65, CONCLUSION). Verma and Somia (Nature 389: 239-242, 1997) review vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that:

> "the Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression . . ."

The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3). Even in 2005, Verma and Weitzman (Annu. Rev. Biochem. 74:711-738, 2005) still state:

> "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to head disease and cancer. It has, therefore, generated great hopes and great hypes, but it has yet to deliver its promised potential" (page 732, top of third paragraph).

Goncalves (BioEssays 27:506-517, 2005) also states:

"Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph).

Johnson-Saliba et al (Curr. Drug. Targets 2:371-99, 2001) concurs stating that "although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery." (Abstract).

Such problems with delivery continue to plague the field of gene therapy. Shoji et al (Current Pharmaceutical Design 10(7): 785-796, 2004) has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non toxicity, non-pathogenicity, non-immunogenicity, [and] non-tumorgenicity."

Furthermore, with regard to promoters in retroviral vectors, attempted gene therapy using said retroviral vectors *ex vivo* (or *in vivo*) has been unsuccessful due to problems involving promoter silencing (possibly due to methylation of sequences in the vicinity of the promoter and/or incorporation of the transgene at the insertion site into condensed chromatin. Bestor (J. Clin. Invest. 105:409-411, 2000) teaches :

"Gene therapy usually depends on a construct or recombinant virus that directs the expression of an agent (protein or RNA) in a particular tissue. Delivery to the target tissue has long been recognized as a difficult problem, as has proper cell type-specific regulation. The existence of gene silencing, the recognition and inactivation of alien genes by target cells, has only been recently recognized as an additional challenge to

gene therapy. Many cases are known in which a transferred gene undergoes a brief period of expression followed by a decline to undetectable levels without the loss of the expression construct. [I]t is now clear that mammalian genes can be inactivated or silent, even in the presence of all factors normally sufficient for their expression, and that cells can detect alterations of their genomes and respond by imposing a strong and heritable silencing effect. [G]ene silencing has already compromised a number of gene transfer efforts and it is likely to represent a barrier to many of the forms of gene therapy currently under development. Even if the delivery and regulation problems can be solved, it is not unlikely that successful gene transfer and tissue-specific expression may be followed by dwindling expression and loss of therapeutic effect unless silencing-resistant expression constructs are developed and used."

The Level of One of Ordinary Skill

The level of skill in the art was high, being that of a Ph.D. or M.D.

The Level of Predictability in the Art

The gene therapy art is a high art, but extremely unpredictable. The unpredictability is manifested in the poor and unpredictable targeting of the gene therapy vectors to target cells, routes of administration, the transient and unpredictable expression of the transgenes in target cells, etc…, all critical for the success of a gene therapy method. Vector based means of introducing DNA into cells for expression have not successfully overcome obstacles related to efficiency of gene delivery and toxicity.

As such, and given the breadth of the claimed invention, and the complexities associated with the breadth and nature of the claimed invention, one skilled in the art would have to turn to the specification for guidance for evidence from Applicant's disclosure in order to practice the claimed methods. However, the as-filed specification does not provide sufficient guidance and/or evidence to overcome and/or resolve the outstanding issues and barriers expressed by the art of record with respect to targeted gene therapy specific for monocytes using an enormous genus of gene transfer vectors, i.e. retroviruses. As such, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is

achieved by a generic heterologous nucleic acid, a generic virus vector and a generic route of delivery as claimed and as contemplated by the as-filed application.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, is considered undue because a person of ordinary skill in the art must discover for themselves the identity of an agent capable of inducing the expression of PTN, how to formulate and deliver such an agent *in vitro* and *in vivo* to specifically target monocytes, and how to target a nucleic acid expression vector encoding PTN, more specifically a retroviral vector, to monocytes *in vivo* so as to cause transdifferentiation of the monocyte into an endothelial cell.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method of transdifferentiating a monocytic cell into an endothelial cell, the method comprising transducing the monocytic cell *in vitro* with a retrovirus expressing PTN such that the monocytic cell transdifferentiates into an endothelial cell, and an endothelial cell produced by said method, is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. **Claims 5-8 are rejected under 35 U.S.C. 102(b)** as being anticipated by Pavlov et al (Mol. Cell. Neurosci. 20(2):330-342, 2002), as evidenced by Hellstrom et al (Development 126(14):3047-3055, 1999; Abstract only).

The instant claims reasonably embrace endothelial cells within an organism.

Pavlov et al teach a transgenic mouse expressing the pleiotrophin (PTN) gene operably linked to the PDGF-beta chain promoter (pg 331, Figure 1).

Pavlov et al do not teach PTN expressed in endothelial cells. However, at the time of the invention, Hellstrom et al taught that PDGF-beta is naturally expressed in endothelial cells.

Thus, absent evidence to the contrary, the endothelial cells of the PTN transgenic mouse inherently express PTN.

Pavlov et al do not teach the endothelial cells are produced by the process of transdifferentiating RAW or THP-1 monocytic cells via a retrovirus expressing PTN. However, the recitation of a process limitation in the claims is not viewed as positively limiting the claimed endothelial cell product absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the endothelial cells were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

7. **Claims 5-8 are rejected under 35 U.S.C. 102(b)** as being anticipated by Abbot et al (Arth. Rheum. 35(4):401-406, 1992; Abstract only) as evidenced by Pufe et al (Arth. & Rheum. 48(3):660-667, 2003; *of record in IDS).

Abbot et al teach isolated synovial endothelial cells. Abbot et al do not teach the endothelial cells express PTN; however, at the time of the invention, Pufe et al taught that synovial endothelial cells endogenously express PTN (entire reference, e.g. Figure 3).

Abbot et al do not teach the endothelial cells are produced by the process of transdifferentiating RAW or THP-1 monocytic cells via a retrovirus expressing PTN. However,

the recitation of a process limitation in the claims is not viewed as positively limiting the claimed endothelial cell product absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the endothelial cells were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. **Claims 1-2 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (U.S. 2002/0098166 A1) in view of Souttou et al (J. Cell. Physiol. 187:59-64, 2001; *of record in IDS) and Powers et al (J. Biol. Chem. 277(16):14153-14158, 2002).

Determining the scope and contents of the prior art.

Havemann et al disclose a method of obtaining endothelial cells, the method comprising culturing mononuclear cells from the blood with a growth factor for endothelial cells, wherein the growth factor is pleiotrophin [0015, 0037]. The mononuclear cells include monocytes [0070]. The mononuclear cells are cultured for further differentiation and proliferation into endothelial precursor cells, developing surface markers increasingly typical of monocytes. These endothelial precursor cells can be isolated, proliferated further and differentiated to give endothelial cells [0069].

The mononuclear cells may be transformed *in vitro* with a gene encoding an effector gene, i.e. a growth factor, to promote the endothelialization of injured vessels or angiogenesis [0032, 0047, 0075, 0191], wherein the transgene may be unrestrictedly activatable, and activation of the activation sequence is self-enhancing [0042], and wherein the transgene is encoded by a viral vector [0049].

Havemann et al do not disclose *ipsis verbis* that the viral vector to transfect the mononuclear cells to be a retroviral vector; however, Havemann et al disclose that those of ordinary skill in the prior art recognize retroviral vectors are used to express an active compound [0002, 0004], and discloses the use of retroviral elements for the expression vector [0124-0125].

Thus, absent evidence to the contrary, those of ordinary skill in the art would reasonably conclude the viral vector to transfect the mononuclear cells reasonably embraces retroviral vectors.

Havemann et al does not teach the pro-angiogenic effector transgene to encode PTN. However, at the time of the invention, Souttou et al taught that PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation (pg 64, col. 1, last ¶).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in development and molecular and cellular biology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

The instantly claimed invention is predicated on the observation that monocytes differentiate into endothelial cells when stimulated by/exposed to PTN. However, the scientific concept that mononuclear cells [which includes monocytes] may differentiate into endothelial cells via stimulation by/exposure to PTN was previously taught by Havemann et al.

The instant claims require the endothelial cell progenitors to express PTN, thereby promoting differentiation into endothelial cells. However, the art recognized that PTN has autocrine and paracrine stimulatory activities in cells expressing both PTN and the PTN receptor

(Powers et al, pg 14155, col. 1, ¶4). While Havemann et al do not teach *ipsis verbis* that the mononuclear cells/monocytes express the PTN receptor, those of ordinary skill in the art would reasonably understand that the PTN receptor is necessarily present because the mononuclear cells/monocytes are disclosed to respond to PTN to give rise to endothelial cells. Thus, the expression of an effector transgene in the mononuclear cells [which includes monocytes] (Havemann) encoding PTN (Souttou) would be reasonably expected to achieve autocrine and paracrine stimulatory activities (Powers), promoting the differentiation of the mononuclear cells into endothelial cells (Havemann).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the transgene encoding a first pro-angiogenic growth factor as taught by Havemann et al with a transgene encoding a second pro-angiogenic growth factor, specifically the PTN growth factor as taught by Souttou et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute the transgene encoding a first pro-angiogenic growth factor growth factor for promoting angiogenesis with a transgene encoding a second pro-angiogenic growth factor, specifically the PTN growth factor, because Souttou et al teach that PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

9. **Claim 3 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (U.S. 2002/0098166 A1) in view of Souttou et al (2001; *of record in IDS) and Powers et al (J. Biol. Chem. 277(16):14153-14158, 2002), as applied to Claims 1-2 above, and in further view of Kume et al (Gene Therapy 7:1193-1199, 2000).

Determining the scope and contents of the prior art.

Neither Havemann et al, Souttou et al nor Powers et al teach the retrovirus expression vector to be a bicistronic retrovirus. However, at the time of the invention, Kume et al taught the use of bicistronic retroviral vectors containing a marker gene, e.g. green fluorescent protein.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector as taught by Kume et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)" When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector, because Kume et al teach that the bicistronic retroviral expression vector comprising a marker gene is a powerful tool for detailed analysis of transduced cells in conjunction with lineage differentiation, greatly facilitates

developing and improving gene transfer strategies, as well as allowing the artisan to visualize transduced cells that have subsequently been transplanted into a host subject (Abstract; pgs 1196-1197, joining ¶).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

10. **Claim 4 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (U.S. 2002/0098166 A1) in view of Souttou et al (2001; *of record in IDS), Powers et al (J. Biol. Chem. 277(16):14153-14158, 2002) and Kume et al (Gene Therapy 7:1193-1199, 2000), as applied to Claims 1-3 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (U.S. Patent 6,309,848) and Eslami et al (J. Vasc. Surg. 34:923-929, 2001).

Determining the scope and contents of the prior art.

Neither Havemann et al, Souttou et al, Powers et al nor Kume et al teach the monocytes to be THP-1 monocytes. However, at the time of the invention, Pufe et al taught that THP-1 cells are responsive to PTN stimulation (pg 665, Figure 6).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

Applicant's intended use of the monocytes transfected with a nucleic acid encoding PTN, thereby inducing differentiation into endothelial cells comprises promoting neovascularization to treat diseases such as ischemia by enhancing or promoting the activity of PTN (pg 8, ¶3).

At the time of the invention, THP-1 monocyte cells were recognized in the art to be useful for implantation into a host subject (Howett et al; col. 17, Example 5) and capable of binding to injured human vein grafts (Eslami et al).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first mononuclear/monocyte cell as taught by Havemann et al with a second monocyte cell, specifically THP-1 as taught by Pufe et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)" When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a first mononuclear/monocyte cell with a second monocyte cell, specifically THP-1, because THP-1 cells are known in the art to be responsive to PTN (Pufe), adhere to injured vein grafts (Eslami), and thus the ordinary artisan has a reasonable expectation that THP-1 cells transfected with a transgene encoding PTN (Havemann, Souttou, Pufe) would adhere at sites of ischemia, thereby expressing the pro-angiogenic growth factor, PTN, and promote the endothelialization of injured vessels or angiogenesis (Havemann, Souttou).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633